application of direct measurements of change in cartilage on MRI. The design of MRI-based efficacy studies includes decisions on sample size, based on estimations of statistical power derived from prior data or expectations concerning progression. The sample size depends on (a) the expected rate of progression in participants treated with placebo, (b) the minimum size of drug effect judged to be clinically relevant, or rate of progression expected in the active treatment arm(s), (c) the variation in progression rate that occurs between participants, and (d) the precision of the measurement technique. Despite results from older studies in persons with knee OA suggesting rates of change for cartilage volume loss in the range of 5−7% per year, more recent studies including from the OAI have produced more conservative estimates in the range of 1−3% per year with substantive variability. To date despite major advances in measurement methods, structure-modifying efficacy has not been convincingly demonstrated for any of the existing pharmacologic agents. Current trials have wanted for more responsive outcome measures both for symptoms and structure in order to identify change.
Methods: Thus conservative study designs based on large x-ray and MRI progression series currently in the public domain require large sample sizes. If we could confidently design studies based on smaller sample sizes and/or shorter study durations, this would reduce the resource implications for MRI based interventional studies.
Results: An increase in the study power could be gained by selecting participants that have features that predict rapid progression in future studies. Several studies have suggested that baseline clinical, biomarker and imaging features are predictive of more rapid progression of cartilage loss in the medial compartment of the knee. These include increased body mass index (BMI), an increased level of type II collagen C-terminal degradation products detected in the urine, the presence of varus malalignment at the tibiofemoral joint, the presence on MRI of subchondral bone marrow lesions or meniscal abnormalities.
Conclusions: These studies that stratify risk of OA progression will be discussed along with their implications for screening failure rates in clinical trials.

I-7 PLACEBO RESPONSE IN OA TRIALS

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Purpose: Clinical evidence of non-specific treatment effects, often termed "placebo effect", has been documented in a wide range of conditions. Such non-specific benefits could result from a patient's response to observation and assessment (Hawthorne effect), the administration of a therapeutic treatment or ritual (placebo treatment), or the patient-practitioner interaction. Randomised controlled trials (RCTs) to investigate the benefits of a treatment attempt to take into account such non-specific effects by use of a placebo control. However, some investigators have questioned whether the placebo effect exists at all, preferring to explain improvements from baseline on placebo in terms of natural disease remission or chance regression to the mean. Recently we undertook a systematic review and meta-analysis of RCTs in OA to determine whether there is evidence for placebo effects in OA and to examine potential determinants of the size of such effects.
Methods: A systematic literature search was undertaken using Medline, EMBASE, Scientific Citation Index, CINAHL and Cochrane Library. Randomised placebo controlled trials in OA were included. The placebo effect was estimated as the effect size (ES) – the standard mean difference between baseline and endpoint. This was compared with the ES obtained from untreated (observation) controls. ES for pain was the primary outcome. Statistical pooling was undertaken as appropriate and 95% confidence interval (CI) was used for comparison. Quality of trials was assessed and potential determinants of placebo effect were examined using multiple regression analysis. Partial regression coefficient (β) was used to present the adjusted size of the association.
Results: We identified 198 trials with 193 placebo groups (16,364 patients) and 14 untreated control groups (1,167 patients) that met our inclusion criteria. These included a range of therapies (non-pharmacological, pharmacological and surgical treatments). The following results were obtained:

1. Placebo was effective at relieving pain (ES = 0.51, 95% CI 0.46, 0.55). This effect was superior to untreated control (ES = 0.03, 95% CI −0.13, 0.18), supporting placebo as a real entity.
2. Placebo also improved function (ES = 0.49, 95% CI 0.44, 0.54) and stiffness (ES = 0.43, 95% CI 0.38, 0.49), but the highest ES was for physician global assessment (ES = 0.66, 95% CI 0.53, 0.78). No improvements were seen for more objective measures such as quadriceps strength, knee circumference or range of movement.
3. Placebo ES for pain relief was higher with treatments that had a larger effect, perhaps reflecting greater expectancy of efficacy from the patient.
4. Placebo ES increased as baseline pain and sample size increased.
5. Route of delivery affected placebo ES for pain, with highest effects seen when given by injection (higher with multiple than single injections), needling, and topical application.
6. Placebo ES for pain was highest for hand OA (0.80, 95% CI 0.65, 0.96), intermediate for knee OA (0.54, 95% CI 0.49, 0.6) and lowest for hip OA (0.37, 95% CI 0.21, 0.53) perhaps implying that hip OA is more severe disease and less amenable to non-specific effects.

Conclusions: Although regarded largely as a "nuisance" in RCTs, it is apparent that non-specific effects of treatment in OA confer greater benefit in terms of symptom improvement than the effect derived from the more specific effect of any one treatment. This has clear implications for design of RCTs. More importantly, however, it emphasises the potential major role for non-treatment effects in the medical care of people with OA and should encourage us to investigate ways of optimising such benefits.

I-8 OARSI-OMERACT SET OF CRITERIA IN KNEE/HIP OSTEOARTHRITIS TO BE USED AS A HARD ENDPOINT IN CLINICAL TRIALS EVALUATING POTENTIAL DISEASE-MODIFYING DRUGS

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Purpose: Little is known about the natural course of deterioration of pain, physical function or joint structure as a result of hip or knee osteoarthritis. An international OARSI/OMERACT working group was created; the objectives are to develop pain, physical function and structure states that represent the progression from early to late disease for individuals with OA of the hip and knee. These states are planned to be used as a "hard endpoint" in potential disease-modifying drug trials, with some states defining "heoretical need for total joint replacement".
Methods: New questionnaires were created to assess pain and functional impairment. Structural assessments have been compared and structural severity was defined as joint space width loss on radiographs. A large multicenter study is ongoing to assess these criteria.
Results: Work is ongoing. Current results will be presented at the OARSI meeting.
Conclusions: The final objective will be to combine the 3 domains (pain, function and structure) and to create a composite index to define states of severity and "theoretical need for total joint replacement" in hip/knee osteoarthritis.

I-9 TRADEOFFS BETWEEN PAIN RELIEF AND THE RISK OF SIDE EFFECTS IN THE TREATMENT OF OA: THE PATIENT'S PERSPECTIVE

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Purpose: Therapeutic decisions in osteoarthritis (OA) often involve trade-offs between accepting risks of side effects and gaining pain relief. Previous studies suggested that the risk of side effects affected treatment preferences but data on patients' preferences for specific trade-offs between pain relief and each side effect of treatment in OA are scarce. Our objectives were (1) to determine patients' maximum acceptable risk increments (MARI) for different adverse effects from OA medication and (2) to identify the predictors of these preferences.
Methods: Participants were individuals diagnosed with OA of the hip or knee according to standard ACR criteria, age 45−74, able to understand English and mentally competent. They were stratified into three categories of disease severity – mild, moderate, and severe. MARI were measured with a probabilistic threshold technique (TT). Risk and pain levels in the TT scenarios were controlled for in a 2×2 randomized factorial design. Clinical, sociodemographic, and psychological characteristics (decisional conflict and locus of control) of the participants were assessed using a self-administered questionnaire.
Results: 196 subjects participated in the study. For most side effects, higher initial-risk levels in the TT tasks were associated with subjects' reports that they would be willing to accept higher additional risks. Depending on the initial level of risk and pain relief, mean MARI ranged from 3% to 5% for heart attack/stroke, 5% to 8% for stomach bleed, 13% to 21% for hypertension, 22% to 33% for fluid retention, and 23% to 35%